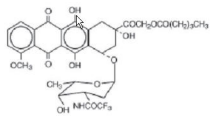
VALSTAR - valrubicin solution, concentrate
Endo Pharmaceuticals Solutions Inc

DESCRIPTION

Valrubicin (N-trifluoroacetyladriamycin-14-valerate), a semisynthetic analog of the anthra-cycline doxorubicin, is a cytotoxic agent with the chemical name, (2*S*-*cis*)-2-[1,2,3,4,6,11-hexahydro-2,5,12-trihydroxy-7-methoxy-6,11-dioxo-4-[[2,3,6-trideoxy-3-[(trifluoroacetyl)amino]-α-L-*lyxo*-hexopyranosyl]oxyl]-2-naphthacenyl]-2-oxoethylpentanoate. Valrubicin is an orange or orange-red powder that is highly lipophilic, soluble in methylene chloride, ethanol, methanol and acetone, and relatively insoluble in water. Its chemical formula is $C_{34}H_{36}F_3NO_{13}$ and its molecular weight is 723.65. The chemical structure is shown in FIGURE 1.

FIGURE 1. Chemical Structure of Valrubicin



VALSTAR™ (valrubicin) Sterile Solution for Intravesical Instillation is intended for intra-vesical administration in the urinary bladder. It is supplied as a nonaqueous solution that should be diluted before intravesical administration. Each vial of VALSTAR contains valrubicin at a concentration of 40 mg/mL in 50% polyoxyl castor oil/50% dehydrated alcohol, USP without preservatives or other additives. The solution is sterile and nonpyrogenic.

CLINICAL PHARMACOLOGY

Mechanism of Action: Valrubicin is an anthracycline that affects a variety of inter-related biological functions, most of which involve nucleic acid metabolism. It readily penetrates into cells, where it inhibits the incorporation of nucleosides into nucleic acids, causes extensive chromosomal damage, and arrests cell cycle in G_2. Although valrubicin does not bind strongly to DNA, a principal mechanism of its action, mediated by valrubicin metabolites, is interference with the normal DNA breaking-resealing action of DNA topoisomerase II.

Pharmacokinetics after Intravesical Administration of VALSTAR: When 800 mg VALSTAR was administered intravesically to patients with carcinoma *in situ*, VALSTAR penetrated into the bladder wall. The mean total anthracycline concentration measured in bladder tissue exceeded the levels causing 90% cytotoxicity to human bladder cells cultured *in vitro*. During the two-hour dose-retention period, the metabolism of VALSTAR to its major metabolites N-trifluoroacetyladriamycin and N-trifluoroacetyladriamycinol was negligible. After retention, the drug was almost completely excreted by voiding the instillate. Mean percent recovery of VALSTAR, N-trifluoroacetyladriamycin, and total anthracyclines in 14 urine samples from six patients was 98.6%, 0.4%, and 99.0% of the total administered drug, respectively. During the two-hour dose-retention period, only nanogram quantities of VALSTAR were absorbed into the plasma. VALSTAR metabolites N-trifluoroacetyladriamycin and N-trifluoroacetyladriamycinol were measured in blood.

Total systemic exposure to anthracyclines during and after intravesical administration of VALSTAR is dependent upon the condition of the bladder wall. The mean $AUC_{0\text{-}6\ hours}$ (total anthracyclines exposure) for an intravesical dose of 900 mg of VALSTAR administered 2 weeks after transurethral resection of bladder tumors (n=6) was 78 nmol/L•hr. In patients receiving 800 mg of VALSTAR 5 to 51 minutes after typical (n=8) and extensive (n=5) transurethral resection of bladder tumors (TURBs), the mean $AUC_{0\text{-}6\ hours}$ values for total anthracyclines were 409 and 788 nmol/L•hr, respectively. The $AUC_{0\text{-}6\ hours}$ total exposure to anthracyclines was 18,382 nmol/L•hr in one patient who experienced a perforated bladder following a transurethral resection that occurred 5 minutes before administration of an intravesical dose of 800 mg of VALSTAR. Administration of a comparable intravenous dose of VALSTAR (600 mg/m^2; n=2) as a 24-hour infusion resulted in an $AUC_{0\text{-}6\ hours}$ for total anthracyclines of 11,975 nmol/L•hr. These results are shown in FIGURE 2.

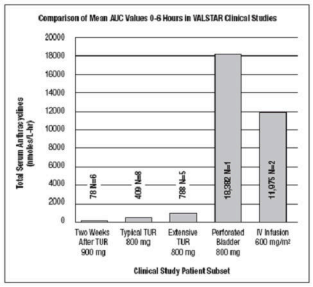


FIGURE 2. Comparison of Mean AUC0-6 hours in VALSTAR Clinical Studies (N=number of patients)

The patient with a perforated bladder who received 800 mg of VALSTAR intravesically developed severe leukopenia and neutropenia approximately two weeks after drug administration. Systemic hematologic toxicity from VALSTAR was not seen after an intravesical dose of 800 mg of VALSTAR unless perforation of the urinary bladder occurred.

CLINICAL TRIALS

VALSTAR has been administered intravesically to a total of 230 patients with transitional cell carcinoma of the bladder, including 205 patients who received multiple weekly doses ranging from 200 to 900 mg. One hundred seventy-nine of the 205 patients received the approved dose and schedule of 800 mg weekly for multiple weeks.

In the 90 study patients with BCG-refractory carcinoma *in situ* (CIS), 70% had received at least 2 courses of BCG and 30% had received one course of BCG and at least one additional course of treatment with another agent(s) - e.g., mitomycin, thiotepa, or interferon. VALSTAR was administered beginning at least two weeks after transurethral resection and/or fulguration. After intravesical administration of VALSTAR, 16 patients (18%) had a complete response documented by bladder biopsies and cytology at 6 months following initiation of therapy. Median duration of response from start of treatment varied according to the method of analysis (13.5 months if measured to last bladder biopsy without tumor and 21 months if measured until time of documented recurrence). A retrospective analysis in the 16 patients with complete response to VALSTAR demonstrated that time to recurrence of their disease after treatment with VALSTAR was longer than time to recurrence after previous courses of intravesical therapy.

Of the 90 patients with BCG-refractory CIS, 11% (10 patients) developed metastatic or deeply-invasive bladder cancer during follow-up; four of these patients, none who underwent cystectomy, died with metastatic bladder cancer and six were found to have developed stage progression to deeply-invasive disease (T3), with lymph node involvement in one patient, at the time of cystectomy. It is difficult to ascertain to what extent the development of advanced bladder cancer in these patients was due to the delay in cystectomy required to receive treatment with VALSTAR (3 months was the time of follow-up to determine response), as cystectomy was often delayed or was never performed despite failure of treatment with VALSTAR. In the 10 patients documented to have invasive bladder cancer or metastatic disease, the delay between the time of treatment failure (when cystectomy should have been performed) and cystectomy or documentation of advanced bladder cancer was a median of 17.5 months.

INDICATIONS AND USAGE

VALSTAR is indicated for intravesical therapy of BCG-refractory carcinoma *in situ* (CIS) of the urinary bladder in patients for whom immediate cystectomy would be associated with unacceptable morbidity or mortality.

CONTRAINDICATIONS

VALSTAR is contraindicated in patients with known hypersensitivity to anthracyclines or polyoxyl castor oil.

Patients with concurrent urinary tract infections should not receive VALSTAR.

VALSTAR should not be administered to patients with a small bladder capacity, i.e., unable to tolerate a 75 mL instillation.

WARNINGS

Patients should be informed that VALSTAR has been shown to induce complete response in only about 1 in 5 patients with BCG-refractory CIS, and that delaying cystectomy could lead to development of metastatic bladder cancer, which is lethal. The exact risk of developing metastatic bladder cancer from such a delay may be difficult to assess (See CLINICAL TRIALS) but increases the longer cystectomy is delayed in the presence of persisting CIS. **If there is not a complete response of CIS to treatment after 3 months or if CIS recurs, cystectomy must be reconsidered.**

VALSTAR should not be administered to patients with a perforated bladder or to those in whom the integrity of the bladder mucosa has been compromised (see PRECAUTIONS and CLINICAL PHARMACOLOGY, Pharmacokinetics Figure 2).

In order to avoid possible dangerous systemic exposure to VALSTAR for the patients undergoing transurethral resection of the bladder, the status of the bladder should be evaluated before the intravesical instillation of drug. In case of bladder perforation, the administration of VALSTAR should be delayed until bladder integrity has been restored.

VALSTAR should be administered under the supervision of a physician experienced in the use of intravesical cancer chemotherapeutic agents.

PRECAUTIONS

General: Aseptic techniques must be used during administration of intravesical VALSTAR to avoid introducing contaminants into the urinary tract or traumatizing unduly the urinary mucosa.

Information for Patients: Patients should be informed that VALSTAR has been shown to induce complete responses in only about 1 in 5 patients, and that delaying cystectomy could lead to development of metastatic bladder cancer, which is lethal. They should discuss with their physician the relative risk of cystectomy versus the risk of metastatic bladder cancer (see CLINICAL TRIALS) and be aware that the risk increases the longer cystectomy is delayed in the presence of persisting CIS.

Patients should be informed that the major acute toxicities from VALSTAR are related to irritable bladder symptoms that may occur during instillation and retention of VALSTAR and for a limited period following voiding. For the first 24 hours following administration, red-tinged urine is typical. Patients should report prolonged irritable bladder symptoms or prolonged passage of red-colored urine immediately to their physician.

Women of childbearing potential should be advised not to become pregnant during treatment. Men should be advised to refrain from engaging in procreative activities while receiving therapy with VALSTAR. All patients of reproductive age should be advised to use an effective contraception method during the treatment period.

Irritable Bladder Symptoms: VALSTAR should be used with caution in patients with severe irritable bladder symptoms. Bladder spasm and spontaneous discharge of the intravesical instillate may occur; clamping of the urinary catheter is not advised and, if performed, should be executed under medical supervision and with caution.

Drug Interactions: Because systemic exposure to VALSTAR is negligible following intravesical administration, the potential for drug interactions is low. No drug interaction studies were conducted.

Carcinogenesis, Mutagenesis, Impairment of Fertility: The carcinogenic potential of VALSTAR has not been evaluated, but the drug does cause damage to DNA *in vitro*. VALSTAR was mutagenic in *in vitro* assays in *Salmonella typhimurium* and *Escherichia coli*. VALSTAR was clastogenic in the chromosomal aberration assay in CHO cells. Studies of the effects of VALSTAR on male or female fertility have not been done.

Pregnancy: Pregnancy Category C. Valrubicin can cause fetal harm if a pregnant woman is exposed to the drug systemically. Such exposure could occur after perforation of the urinary bladder during valrubicin therapy. Daily intravenous doses of 12 mg/kg (about one sixth of the recommended human intravesical dose on a mg/m^2 basis) given to rats during fetal development caused fetal malformations. A dose of 24 mg/kg (about one third the recommended human intravesical dose on a mg/m^2 basis) caused numerous, severe alterations in the skull and skeleton of the developing fetuses. This dose also caused an increase in fetal resorptions and a decrease in viable fetuses. Thus, valrubicin is embryo-toxic and teratogenic. There are no preclinical studies of the effects of intra-vesical valrubicin on fetal development and no adequate and well controlled studies of valrubicin in pregnant women. If valrubicin is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. It should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women who might become pregnant should be advised to avoid doing so during therapy with VALSTAR.

Nursing Mothers: It is not known whether VALSTAR is excreted in human milk. Nevertheless, the drug is highly lipophilic and any exposure of infants to VALSTAR could pose serious health risks. Women should discontinue nursing before the initiation of VALSTAR therapy.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: Because carcinoma *in situ* of the bladder generally occurs in older individuals, 85% of the patients enrolled in the clinical studies of VALSTAR were more than 60 years of age (49% of the patients were more than 70 years of age). In the primary efficacy studies, the mean age of the population was 69.5 years. There are no specific precautions regarding use of VALSTAR in geriatric patients who are otherwise in good health.

ADVERSE REACTIONS

Approximately 84% of patients who received intravesical VALSTAR in clinical studies experienced local adverse events, but approximately half of the patients reported irritable bladder symptoms prior to treatment. The local adverse reactions associated with VALSTAR usually occur during or shortly after instillation and resolve within 1 to 7 days after the instillate is removed from the bladder.

TABLE 1 displays the frequency of the local adverse experiences at baseline and during treatment among 170 patients who received 800 mg doses of VALSTAR™ (valrubicin) Sterile Solution for Intravesical Instillation in a multiple-cycle treatment regimen. Only 7 of 143 patients who were scheduled to receive six doses failed to receive all of the planned doses because of the occurrence of local bladder symptoms.

TABLE 1
Occurrence of Local Adverse Reactions Before and During Treatment with Intravesical VALSTAR (% of Patients)

	Patients Who Received Multiple-Cycle Treatment Regimen at 800 mg/dose (N=170)	
Reaction	**Before Treatment**	**During 6-week Course of Treatment**
ANY LOCAL BLADDER SYMPTOM	45%	88%
Urinary Frequency	30%	61%
Dysuria	11%	56%
Urinary Urgency	27%	57%
Bladder Spasm	3%	31%
Hematuria	11%	29%

Bladder Pain	6%	28%
Urinary Incontinence	7%	22%
Cystitis	4%	15%
Nocturia	2%	7%
Local Burning Symptoms – Procedure Related	0%	5%
Urethral Pain	0%	3%
Pelvic Pain	1%	1%
Hematuria (Gross)	0%	1%

Most systemic adverse events associated with use of VALSTAR have been mild in nature and self-limited, resolving within 24 hours after drug administration. TABLE 2 displays the adverse events other than local bladder symptoms that occurred in 1% or more of the 230 patients who received at least one dose of VALSTAR (200 to 900 mg) in a clinical trial. It cannot be determined whether these events are drug-related.

TABLE 2
Most Commonly Reported Systemic Adverse Reactions
Following Intravesical Administration of VALSTAR (% of Patients)

Body System **Preferred Term**	**All Patients Who Received VALSTAR** **(N = 230)**
Body as a Whole	
Abdominal Pain	5%
Asthenia	4%
Back Pain	3%
Chest Pain	3%
Fever	2%
Headache	4%
Malaise	4%
Cardiovascular	
Vasodilation	2%
Digestive	
Diarrhea	3%
Flatulence	1%
Nausea	5%
Vomiting	2%
Hemic and Lymphatic	
Anemia	2%
Metabolic and Nutritional	
Hyperglycemia	1%
Peripheral Edema	1%
Musculoskeletal	
Myalgia	1%
Nervous	
Dizziness	3%
Respiratory	
Pneumonia	1%
Skin and Appendages	
Rash	3%
Urogenital	
Hematuria (miscroscopic)	3%
Urinary Retention	4%
Urinary Tract Infection	15%

Adverse reactions other than local reactions that occurred in less than 1% of the patients who received VALSTAR intravesically in clinical trials are listed below. This list includes only adverse reactions that were suspected of being related to treatment.
Digestive System: Tenesmus.
Metabolic and Nutritional: Nonprotein nitrogen increased.
Skin and Appendages: Pruritus.
Special Senses: Taste loss.
Urogenital System: Local skin irritation, poor urine flow, and urethritis.
Inadvertent paravenous extravasation of VALSTAR was not associated with skin ulceration or necrosis.

OVERDOSAGE
There is no known antidote for overdoses of VALSTAR. The primary anticipated complications of overdosage associated with intravesical administration would be consistent with irritable bladder symptoms.
Myelosuppression is possible if VALSTAR is inadvertently administered systemically or if significant systemic exposure occurs following intravesical administration (e.g., in patients with bladder rupture/perforation). The maximum tolerated dose in humans by either intraperitoneal or intravenous administration is 600 mg/m^2. Dose limiting toxicities are leukopenia and neutropenia, beginning within 1 week of dose administration, with nadirs by the second week, and recovery generally by the third week. If VALSTAR is administered when bladder rupture or perforation is suspected, weekly monitoring of complete blood counts should be performed for 3 weeks.

DOSAGE AND ADMINISTRATION
VALSTAR is recommended at a dose of 800 mg administered intravesically once a week for six weeks. Administration should be delayed at least two weeks after transurethral resection and/or fulguration. For each instillation, four 5 mL vials (200 mg valrubicin/5 mL vial) should be allowed to warm slowly to room temperature, but should not be heated. Twenty milliliters of VALSTAR should then be withdrawn from the four vials and diluted with 55 mL 0.9% Sodium Chloride Injection, USP providing 75 mL of a diluted VALSTAR solution. A urethral catheter should then be inserted into the patient's bladder under aseptic conditions, the bladder drained, and the diluted 75 mL VALSTAR solution instilled slowly via gravity flow over a period of several minutes. The catheter should then be withdrawn. The patient should retain the drug for two hours before voiding. At the end of two hours, all patients should void. (Some patients will be unable to retain the drug for the full two hours.) Patients should be instructed to maintain adequate hydration following treatment.
Patients receiving VALSTAR for refractory carcinoma *in situ* must be monitored closely for disease recurrence or progression. Recommended evaluations include cystoscopy, biopsy, and urine cytology every 3 months.

Administration Precautions: As recommended with other cytotoxic agents, caution should be exercised in handling and preparing the solution of VALSTAR. Contact toxicity, common and severe with other anthracyclines, is not typical with VALSTAR and, when observed, has been mild. Skin reactions may occur with accidental exposure, and the use of gloves during dose preparation and administration is recommended. Irritation of the eye has also been reported with accidental exposure. If this happens, the eye should be flushed with water immediately and thoroughly.
VALSTAR sterile solution contains polyoxyl castor oil, which has been known to cause leaching of di(2-ethylhexyl) phthalate (DEHP) a hepatotoxic plasticizer, from polyvinyl chloride (PVC) bags and intravenous tubing. VALSTAR solutions should be prepared and stored in glass, polypropylene, or polyolefin containers and tubing. It is recommended that non-DEHP containing administration sets, such as those that are polyethylene-lined, be used.
Procedures for proper handling and disposal of anticancer drugs should be used.[1-7] Spills should be cleaned up with undiluted chlorine bleach.

Preparation for Administration: VALSTAR Sterile Solution for Intravesical Instillation is a clear red solution. It should be visually inspected for particulate matter and discoloration prior to administration. At temperatures below 4°C, polyoxyl castor oil may begin to form a waxy precipitate. If this happens, the vial should be warmed in the hand until the solution is clear. If particulate matter is still seen, VALSTAR should not be administered.

Stability: Unopened vials of VALSTAR are stable until the date indicated on the package when stored under refrigerated conditions at 2°-8°C (36°-46°F). Vials should not be heated. VALSTAR diluted in 0.9% Sodium Chloride Injection, USP for administration is stable for 12 hours at temperatures up to 25°C (77°F). Since compatibility data are not available, VALSTAR should not be mixed with other drugs.

HOW SUPPLIED
VALSTAR Sterile Solution for Intravesical Instillation is a clear red solution in polyoxyl castor oil/dehydrated alcohol, USP, containing 40 mg valrubicin per mL. VALSTAR Sterile Solution for Intravesical Instillation is available in single-use, clear glass vials, individually packaged in the following sizes:

NDC 67979-001-01	Carton of 4, 5 mL Single-Use Vials (200 mg/5 mL)

Store vials under refrigeration at 2°-8°C (36°-46°F) in the carton. DO NOT FREEZE.
For more information, call 1-800-462-3636
Manufactured for:
Endo Pharmaceuticals Solutions Inc.
Chadds Ford, PA 19317
By:
Ben Venue Laboratories, Inc.
Bedford, OH 44146
Valstar™ is a trademark of Endo Pharmaceuticals.

109244 October 2009

REFERENCES

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3. *National Study Commission on Cytotoxic Exposure-Recommendations for Handling Cytotoxic Agents*. Available from Louis P. Jeffrey, ScD., Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.

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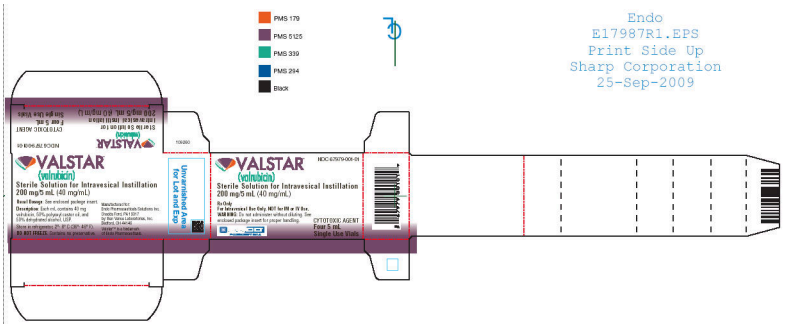
PACKAGE LABEL – PRINCIPLE DISPLAY PANEL – VIAL LABEL

PACKAGE LABEL – PRINCIPLE DISPLAY PANEL – CARTON – 4 VIALS



PACKAGE LABEL – PRINCIPLE DISPLAY PANEL – CARTON – 24 VIALS